REMARKS

The Official Action dated January 18, 2011 has been carefully considered. Accordingly, it is believed that the present Amendment responds fully to the outstanding matters and places this application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 1, 33 and 61 are amended to recite the vesicles are formed of a lipid bilayer membrane as described in the specification, for example, at page 16, lines 11-13. It is believed the present changes do not involve any introduction of new matter, whereby entry is in order and is respectfully requested.

Claims 1, 5-11, 13, 15, 17-22, 33, 34, 36, 37, 39 and 41-65 are pending. Applicants request rejoinder of claims 6, 7, 9-11, 13, 15, 17-22, 33, 34, 36, 37, 39 and 41-62, which all depend directly or indirectly from claim 1, upon allowance of claim 1.

In the Official Action, claims 1, 8 and 63-65 were finally rejected under 35 U.S.C. §103(a) as being obvious and unpatentable over the Hamalainen et al U.S. Patent Publication No. 2002/0019019 A1 in view of the Keinanen et al U.S. Patent No. 6,235,535, the Mirkin et al U.S. Patent No. 6,361,944 and the Kataoka et al U.S. Patent Publication No. 2005/0079195 A1, while claim 5 was rejected as being obvious and unpatentable over these references and further in view of the Brederhorst et al WO 02/081739 A2. The Examiner asserted that it would have been obvious to employ liposomes associated with membrane proteins in the method of Hamalainen since Keinanen teaches that such liposome structures can be used as recognition surfaces in biosensors, to employ the immobilization method of Mirkin, in which vesicles are mobilized on a surface via hybridization of linker oligonucleotides, and to provide multi-layer micelle (vesicles/liposomes) as taught by Kataoka. The Examiner relied on Brederhorst as teaching linkers such as oligonucleotides can be attached to vesicles via a covalent bond using a

functional group. The Examiner also asserted that since Hamalainen, Keinanen and Kataoka all relate to liposomal structures on a surface, the advantage of Kataoka can be applied to Hamalainen and Keinanen. Finally, the Examiner asserted that one of ordinary skill would have been motivated to use the assembling method of Mirkin to obtain the advantage of allowing systematic control for making a designed and well defined biosensor surface structure.

This rejection is traversed and reconsideration is respectfully requested. Applicants submit that the cited combinations of references provide no apparent reasoning for one of ordinary skill in the art to combine their teachings to result in a multilayer structure as recited in claim 1. Moreover, in view of the significant differences in the assembly and method of Mirkin as compared with the present invention, the cited combination of references does not result in the structures as presently claimed.

That is, according to claim 1, the invention is directed to a biologically-functional, surface-immobilized multilayer structure comprising a plurality of vesicles formed of a lipid bilayer membrane and sufficiently spaced apart from the surface. A portion of the vesicles are directly attached to the structure by binding surface-immobilized linkers with vesicle-attached linkers and a portion of the vesicles are attached to the structure by binding vesicle-attached linkers to vesicle-attached linkers of other vesicles, so as to provide the structure with two or more vesicle layers. The surface-immobilized linkers and the vesicle-attached linkers comprise oligonucleotides and binding of one linker to another linker is mediated through hybridization of the linker oligonucleotides. At least a selected population of the vesicles comprise a biologically active compound which provides the structure with biological functionality.

Thus, the multilayer structure according to claim 1 comprises lipid bilayer-comprising vesicles and attached linkers arranged to provide a multilayered immobilized structure by means

of hybridization to control the distance of the vesicles from the surface. In contrast, Hamalainen discloses at paragraphs [0070] – [0079] the structure and preparation of a sensor surface. As described in paragraph [0070], the sensor surface has a hydrogel matrix coating coupled to the top of the sensor surface, the hydrogel matrix coating has a plurality of functional groups, and at least two different types of liposomes are bonded to the functional groups at discrete and noncontiguous locations on the hydrogel matrix coating. The sensor surface is useful for studying drug candidate interactions with the liposomes using a mass sensing technique such as surface plasmon resonance technology. However, Applicants find no teaching by Hamalainen of surface-immobilized linkers serving to build several vesicle layers, particularly layers of vesicles formed of lipid bilayers, or that such vesicles include bioactive compounds, as defined in claim 1.

On the other hand, Keinanen discloses a fluorescence-based immunoassay with receptor (antibody) molecules anchored to the lipid membrane of a liposome for potential use in a biosensor. Keinanen does not provide any teaching directed to a surface immobilized structure with multiple layers of vesicles and, to the contrary, Keinanen simply reviews the prior art of lipid bilayers.

Kataoka describes a lipid vesicle surface of crosslinked micelles to be used for drug delivery wherein active agents associated with the surface employ the micelle structure for controlled release in order to improve articles like contact lenses and intraocular lenses. See page 10, paragraphs [0160]-[0165]. In contrast, the presently claimed invention employs lipid bilayer-comprising vesicles with attached linkers arranged to form a multilayered immobilized structure by hybridization to control of the distance of the vesicles from the surface. The

multilayers of lipid bilayer-comprising vesicles with attached linkers are clearly and significantly distinguishable from the crosslinked micelles of Kataoka.

Importantly, Mirkin also fails to disclose the vesicle-oligonucleotide linking structures required by present claim 1, or a method for providing such a structure. Mirkin discloses a structure wherein a nucleic acid to be detected is contacted with a substrate having attached oligonucleotides. The oligonucleotides have a sequence complementary to a first portion of the target nucleic acid and once the nucleic acid is bound to the substrate through hydridization, it is contacted with liposomes having attached oligonucleotides which are complementary to a portion of a sequence of the nucleic acid, whereby hybridization of the liposome oligonucleotide occurs. An aggregate probe having an oligonucleotide is then contacted with the assembly and upon attachment of the aggregate probe oligonucleotides to the liposomes as a result of hydrophobic interactions, a detectable change is observed.

The target nucleic acid is therefore required for the Mirkin assembly, and Mirkin does not disclose, as required by claim 1, a portion of the vesicles directly attached to the structure by binding surface-immobilized linkers with vesicle-attached linkers, wherein the surface-immobilized linkers and the vesicle-attached linkers comprise oligonucleotides and binding of one linker to another linker is mediated through hybridisation of said linker oligonucleotides. Rather, Mirkin discloses a vesicle (liposome) is attached to a nucleic acid through hybridization of the nucleic acid and an oligonucleotide attached to the vesicle, and the nucleic acid in turn is attached to a surface through hybridization of the nucleic acid and a surface-attached oligonucleotide. This is a significant difference since the object of Mirkin is to capture the target nucleic acid, while the multilayer structure of claim 1 does not incorporate a target nucleic acid in the surface immobilization of the liposomes.

The following schematic illustrates the difference in the Mirkin structure as compared with the claimed structure:

Mirkin:

Surface Immobilized Oligonucleotide	--	hybridized to	--	target Nucleic Acid	-- hybridized to --	Oligonucleotide attached to Liposome

Claim 1:

Surface Immobilized Oligonucleotide	--	hybridized to	--	Oligonucleotide attached to Vesicle

Thus, combination of Mirkin with Hamalainen, Keinanen and Kataoka does not result in the present claimed structure.

Finally, Brederhorst fails to resolve the deficiencies of Hamalainen, Keinanen, Kaaoka and Mirkin. That is, Bredehorst discloses a technology similar to Mirkin in that a "sandwich structure" is formed (see Fig. 4) wherein captured analyte DNA is contacted with reporter liposomes to generate such a structure, and Bredehorst fails to teach a multilayer structure as recited in claim 1.

In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements of the prior art in the fashion of the claims at issue, *KSR International Co. v. Teleflex, Inc.*, 550 US 398, 418 (2007). In view of the failure of any of the cited references to teach or suggest a multilayer structure wherein a portion of the vesicles formed of a lipid bilayer are directly attached to the structure by binding surface-immobilized linkers with vesicle-attached linkers and a portion of the vesicles are attached to the structure by binding vesicle-attached linkers to vesicle-attached linkers of other vesicles, so as to

provide the structure with two or more vesicle layers, wherein binding of one linker to another linker is mediated through hybridization of the linker oligonucleotides, the cited combinations of references do not provide one of ordinary skill in the art with any apparent reason to combine the known elements of the prior art in the fashion of the claims at issue, and particularly in the fashion of the multilayer structure of claim 1.

To the contrary, one of ordinary skill in the art would have found Hamalainen as teaching immobilized biomolecules and liposomes at discrete and noncontiguous locations, i.e., maintained apart on the surface so interactions between the liposomes and drug candidates can be studied. One of ordinary skill in the art would have had no motivation to anchor the biomolecules to lipid bilayer membranes as employed with the antibodies in Keinanen, or to provide multiple layers of such lipid bilayer membranes. Further, there is simply no suggestion or motivation in Hamalainen to link the liposomes, at discrete and noncontiguous locations, in a multilayered structure with vesicle-attached linkers by hybridization. Quite in contrast, Hamalainen does not provide any suggestion or motivation to associate liposomes with a bioactive agent in a controlled way using a multilayer vesicle structure as required by claim 1, or any recognition that such a structure would lead to advantages for surface sensitive bioactive agents.

It is even more remote for one of ordinary skill in the art of the sensor-related disclosures of Hamalainen and Keinanen to have turn to Kataoka for further guidance and improvement as Kataoka leads to a structure of crosslinked micelles without any membrane, wherein the micelles provide a controlled release from a surface holding a drug. It is evident that the combined teachings of Hamalainen, Keinanen and Kataoka do not lead to the multilayer structure of lipid bilayer-comprising vesicles of the presently claimed invention.

Finally, both Bredehorst and Mirkin are directed to surface immobilized oligonucleotides that 1) hybridize with a target/anlayte DNA, and 2) hybridize with a liposome having a linker of complementary oligonucteotide, to form a sandwich of surface immobilized oligonucleotide – target/analyte – liposome. As illustrated above, the claimed structure is significantly distinguishable from such a sandwich of a target/analyte DNA. The purpose of Bredehorst and Mirkin is principally to bind analytes and improve detecting/reporting functions as introduced by the liposomes or clusters of liposomes as in Bredehorst. The multilayer structure of the present invention, in contrast, is an assembly of a multilayered structure of lipid bilayer vesicles having a bioactive compound associated with the vesicles in order to study the interaction between the bioactive compounds, such as for example a membrane protein, and ligands. Not only are the objectives of the presently claimed invention different from those of Bredehorst and Mirkin, the claimed structure is distinct as well, particularly by the fact that surface-immobilized linkers are directly bonded to vesicle-attached linkers in the structure, without any intermediate analyte DNA.

Thus, Hamalainen/Keinanen/Kataoka do not suggest or recognize that a multilayered structure of lipid bilayer vesicles, some of which vesicles comprise a bioactive agent, may be useful, while Bredehorst/Mirkin proceed in a different direction in which vesicles can be immobilized to a solid support as a consequence as of a captured DNA analyte. Accordingly, the cited combinations of references do not render the multilayer structures of claim 1, 5, 8 and 63-65 obvious and the rejections under 35 U.S.C. §103 have been overcome. Reconsideration is respectfully requested.

Claims 1-5, 8 and 63-65 were also provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-22 of co-pending

application Serial No. 10/590,877. Although this is a provisional rejection, Applicants traverse the rejection on the basis that the present claims 1, 5, 8 and 63-65 are patentably distinct from claims 1-22 of the co-pending application. That is, as noted above, the present claims are directed to a biologically-functional, surface-immobilized multilayer structure which comprises a plurality of vesicles sufficiently spaced apart from said surface, wherein a portion of the vesicles are directly attached to the structure by binding surface-immobilized linker oligonucleotides with vesicle-attached linker oligonucleotides and a portion of the vesicles are attached to the structure by binding vesicle-attached linkers to vesicle-attached linkers of other vesicles, so as to provide the structure with two or more vesicle layers. Claims 1-22 of the co-pending application recite an oligonucleotide having at least two hydrophobic anchoring moieties capable of being attached to a lipid membrane. The oligonucleotide structure of the co-pending application increases the stability of a linker attached to a lipid membrane by using a hydrophobic anchoring unit and is not required by and does not render obvious the multilayer structure of lipid vesicles according to the present claims. Accordingly, withdrawal of the obviousness-type double patenting rejection is respectfully requested.

It is believed that the above represents a complete response to Official Action, and places the present application in condition for allowance. In the event there are any outstanding issues relating to this application, the Examiner is urged to telephone the undersigned to efficiently resolve the same. Reconsideration and an early allowance are requested.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 503915.

Respectfully submitted,

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